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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/348,469	07/07/99	SMITH A	06999.0001-0

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EXAMINER
ZARA, J

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary	Application No. 09/348,469	Applicant(s) Smith et al
	Examiner Zara, Jane	Group Art Unit 1635

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *22-40* is/are pending in the application.

Of the above, claim(s) *30 and 31* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *22-29 and 32-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 22-40 are pending in the instant application.

Election/Restriction

Restriction to one of the following invention is required under 35 U.S.C. 121:

I. Claims 22-29 and 32-40, drawn to methods of inserting heterologous gene coding sequences into a eukaryotic host genome, classified in class 435, subclasses 6, 455,468 and 471.

II. Claims 30-31, drawn to an animal and a descendent of an animal comprising a heterologous gene coding sequence, classified in class 800, subclass 8.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the method of inserting heterologous gene coding sequences into a eukaryotic host genome can be used to generate a variety of transgenic organisms.

Because the inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Leslie A. McDonell, Attorney for Applicants on or about March 10, 2000, a provisional election was made to prosecute the invention of Group I, claims 1-29 and 32-40. Affirmation of this election must be made by applicant in replying to this Office action. Claims 30-31 are with drawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Regarding claims 27, 34 and 40, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-29 and 32-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inserting a heterologous gene into an endogenous gene in a mouse embryonic stem cell genome comprising transforming the host cell with a random gene trap vector comprising a heterologous gene coding sequence, a splice acceptor, a polyadenylation signal, and an internal ribosome entry site wherein the heterologous gene coding sequence is expressed in a mouse cell, does not reasonably provide enablement for a method of inserting any heterologous gene into any endogenous gene in any host cell genome in any animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of inserting a heterologous gene coding sequence into an endogenous gene in a eukaryotic cellular host cell genome comprising transforming the host cell with a random gene trap vector comprising a heterologous gene coding sequence, a splice acceptor, a polyadenylation signal, and an internal ribosome entry site or additionally comprising a selectable marker cassette optionally adapted for recombinatorial deletion whereby the heterologous gene coding sequence is expressed in an animal cell. The specification as filed fails

to provide any guidance for a method of inserting any heterologous gene into any endogenous gene in any host cell genome in any animal such that the heterologous gene is expressed in all animals. The specification as filed teaches only the expression of heterologous reporter or selection genes in an *IRES-beta-geo* containing gene trap vector cassette comprising a heterologous gene, a splice acceptor, a polyadenylation signal and an internal ribosome entry site in embryonic stem (ES) cells in mice. One skilled in the art would not accept on its face the examples given of the expression of heterologous marker genes in mice as being representative or correlative of the expression of all heterologous genes in all animals. The specification as filed fails to provide any particular guidance for the expression of all heterologous genes in said gene trap vector comprising the transformation of all host cells in all animals. The quantity of experimentation required to practice the invention over the scope claimed would require the de novo determination of appropriate gene trap vector components which are compatible and functional for the transformation and subsequent expression of heterologous genes in all host cells of all animals, which host cells include somatic cells, totipotent cells and pluripotent cells. Since the specification fails to provide any particular guidance in this regard, and since determination of these factors for a particular gene trap vector is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed. Therefore the invention is not considered to be enabled over the scope claimed.

Claims 35-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of inserting a heterologous gene coding sequence into an endogenous gene in a eukaryotic host cell genome comprising transforming the host cell with a gene trap vector comprising a promoterless heterologous gene, a splice acceptor, a polyadenylation signal, an IRES and a selectable marker cassette located 3' to the heterologous gene sequence, which cassette is optionally adapted for recombinatorial deletion following introduction of the gene trap vector into a host gene.

The specification as filed fails to provide any particular guidance for the construction of gene trap vector which comprises on its 3' end a selectable marker cassette which is optionally adapted for recombinatorial deletion following its introduction into a host gene. The specification as filed teaches the design and construction of a gene trap vector comprising a promoterless heterologous gene, a splice acceptor, a polyadenylation signal and an IRES whereby the heterologous gene is functionally integrated, transcribed and expressed in a mouse embryonic stem cell. One skilled in the art would not accept on its face the examples given for the construction of a gene trap vector, which vector comprises a splice acceptor, a heterologous gene, a polyadenylation signal and an IRES, as being representative or correlative of a vector construct which further comprises (another heterologous) selection marker gene within a cassette which is

optionally adapted for recombinatorial deletion upon transformation into any host gene in view of the lack of guidance in the specification for the construction of a gene trap vector comprising both a deletion cassette which is adjacent and downstream to a separate heterologous gene sequence to be independently and functionally integrated and expressed in any host cell.

The quantity of experimentation required to practice the invention as claimed would require the de novo determination of vector design, construction, stability and cofunctionality of the various parts, and further leading to the successful expression of any heterologous gene in any host cell, whereby a portion of the gene trap vector undergoes recombinatorial deletion while another portion of the vector undergoes functional integration, transcription, translation and expression of a different heterologous gene in any host cell. Since the specification fails to provide any particular guidance in this regard, determination of these factors for a particular gene trap vector comprising all of these parts in a particular host would require undue experimentation to practice the invention claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-29 and 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skarnes in view of the combination of Ghattas et al, Tsukiyama-Kohara et al and Sambrook et al.

The claimed invention is drawn to compositions and methods compositions for inserting a heterologous gene into an endogenous gene in a eukaryotic host cell genome comprising transformation of the host cell with a gene trap vector comprising a promoterless heterologous gene sequence which may be a selectable marker gene, a splice acceptor sequence located 5' to the heterologous gene which permits functional integration of the heterologous gene into a host intron sequence, an internal ribosome entry site (IRES) located between the splice acceptor sequence and the heterologous gene, and a polyadenylation signal located 3' to the heterologous gene sequence.

Skarnes teaches the design and use of entrapment vectors for the generation of transformed eukaryotic host cells, comprising a splice acceptor which is located 5' to a promoterless heterologous reporter gene, which splice acceptor allows for the functional

integration of said heterologous reporter into the intron of the host gene, whereby the polyadenylation signal is provided in the 3' end of the reporter construct, and the expression of the reporter is regulated by the *cis*-acting enhancer, promoter and translational control signals of the endogenous gene (pages 827-828, section entitled *Entrapment Vectors*, also see figure 1, page 828). Skarnes teaches the screening of various eukaryotic host cells following their transformation with such gene trap vectors utilizing reporter genes including lac Z expression patterns in transformed animal cells (page 828, first and second paragraphs on the right).

Skarnes does not teach the incorporation of an internal ribosome entry site into the gene trap vector.

Tsukiyama-Kohara et al and Ghattas et al each teach the identification of sequences which define the internal ribosome entry sites from hepatitis C virus and encephalomyocarditis virus respectively, as well as their use in the initiation of translation of heterologous proteins in the absence of internal promoters.

Tsukiyama-Kohara et al teach the cell free translation of polycistronic HCV genes in a cap independent manner using the shortest IRES sequence obtained from hepatitis C viral RNA (see figure 2 on page 1478; page 1480, the two paragraphs in the section entitled *Identification of an IRES* and see first paragraph of the *Discussion*).

Ghattas et al teach that the IRES of encephalomyocarditis virus can be removed from its viral setting and placed within an expression vector to produce polycistronic mRNAs of

heterologous genes (abstract; page 5852, last three paragraphs on the right-page 5854, see also figures 2 and 3 and table 2).

Sambrook et al teach the contribution of polyadenylation in messenger RNA stability (see page 18.81).

It would have been obvious to one of ordinary skill in the art to construct a gene trap vector comprising a splice acceptor sequence and a heterologous gene sequence, whereby the heterologous gene sequence is located downstream from the splice acceptor sequence because it was known in the art that splice acceptor sequences allow vectors in which they occur, and which vectors further comprise downstream coding gene sequences, to be transcribed as mature, biologically active mRNA when integrated in an active chromosomal locus and transcribed as a contiguous part of premessenger RNA of the choromosomal locus. One of ordinary skill in the art would have been motivated to place a polyadenylation site in a 3' position relative to the heterologous gene coding sequence because polyadenylation signals are routinely found in this position relative to coding sequences on mRNA and contribute to transcript stability, as had been taught in the prior art by Sambrook et al. One of ordinary skill in the art would have expected that inclusion of a polyadenylation signal into the gene trap vector and downstream to a heterologous gene sequence would provide for enhancing the stability of the heterologous gene transcripts of various genes without having to include the poly A signal in addition to the coding sequences for all heterologous genes which are to be inserted into the gene trap vector. One of ordinary skill in the art would have been motivated to incorporate these three components in the

appropriate arrangement within a vector in order to transform a host cell and allow integration of the gene trap cadette into the host genome in order to achieve functional integration and generate stable transcripts in a transformed host cell. One of ordinary skill in the art would have been motivated to use a reporter construct as a heterologous gene in order to test the functionality of the gene trap vector cassette in a host cell and to identify successfully transformed cells from wild type cells and from non-functionally integrated or mutagenized genes within the gene trap vector. One of ordinary skill in the art would have been further motivated to incorporate an IRES sequence into the gene trap vector 5' to the heterologous gene sequence and 3' to the splice acceptor sequence because it was known in the art that IRES sequences are optimally placed in this position in order to allow attachment of a downstream coding region with a cytoplasmic polysomal ribosome for initiating translation in the absence of internal promoters, as had been taught by Tsukiyama-Kohara et al and Ghattas et al. One of ordinary skill in the art would have expected that the inclusion of all of these components within a gene trap vector, a splice acceptor sequence with a downstream internal ribosome entry site, a promoterless heterologous gene sequence and a polyadenylation signal allows for the functional integration, transcription and translation of said heterologous gene coding sequences and the identification of host cells which have been transformed with such a trap vector.

Therefore the invention as whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (703)-***306-5820***. The examiner's supervisory primary examiner is George Elliott who can be contacted at (703)-***308-4003.***

REMY YUCEL, PH.D
PATENT EXAMINER

JZ

March 24, 2000